REMARKS

Applicants have carefully considered the Examiner's Non-Final Office Action, and respectfully request reconsideration of this Application in view of the above amendments and the following remarks.

Claims 11, 16-18, 21-26 and 29-61 have been withdrawn as part of a non-elected invention. Claims 1-10, 12-15, 19, 20, 27 and 28 are currently under consideration. Claim 1 has been amended, and this amendment finds support throughout the specification and in paragraphs [0020], [0025], [0027], [0042], and [0067]. Claim 15 has been amended, and this amendment finds support throughout the specification and in paragraphs [0074] - [0076]. Claim 27 has been amended, and this amendment finds support throughout the specification and in paragraphs [0059] and [0060]. New Claims 62-65 have been added. Support for Claim 62 can be found throughout the specification and in paragraphs [0023], and [0025]; support for Claim 63 can be found throughout the specification and in paragraphs [0002], [0010], [0011], [0023], [0025], and [0027]; support for Claim 64 can be found in paragraphs [0065], [0070], and [0071]; and support for Claim 65 can be found in paragraphs, [0023], [0026], [0065], [0070], [0071], and [0106].

I. CLAIM OBJECTIONS

The Examiner has objected to Claims 1-10, 12-15, 19, 20, 27, and 28 under 35 U.S.C. §112, second paragraph, stating that Claim 1 does not contain a method step that relates the method steps back to the preamble.

In response, Applicants have amended Claim 1 to relate the method steps to the preamble. Applicants submit that Claim 1 is now formal and in condition for allowance.

II. CLAIM REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

The Examiner has rejected Claim 15 under 35 U.S.C. §112, first paragraph, stating that this claim lacks an adequate written description in the specification. Specifically, the Examiner argues that, although the specification describes SEQ ID NO:1 and SEQ ID NO:2, this does not

provide a description of "an isolated oncolytic virus having a sequence at least 95% identical to SEQ ID NO:1" that would satisfy the standards set out in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002).

The Examiner has stated that one alternative for providing an adequate written description of "an isolated oncolytic virus having a sequence at least 95% identical to SEQ ID NO:1", per Lilly, would be to describe a representative number of species. Applicants respectfully submit that such a description is present in the specification. The description of "a sequence at least 95% identical to SEQ ID NO:1" describes a finite number of defined structures.

In order to make the distinction between the claimed structures clearer, Applicants have amended Claim 15 to read "comprising a nucleotide sequence at least 95% identical to SEQ ID NO:1." This emphasizes that, in order for Claim 15 to read on a structure, it may only be a polymer consisting of nucleotides, and that, when compared with SEQ ID NO:1, 95% of the nucleotides must be identical.

Moreover, the specification specifically defines percentage of sequence identity in paragraph [0051] as follows:

> The terms "percentage of sequence identity" as used herein compares two optimally aligned sequences over a comparison window, wherein the portion of the sequence in the comparison window may comprise additions or deletions (i.e. "gaps") as compared to a reference sequence for optimal alignment of the two sequences being compared. The percentage identity is calculated by determining the number of positions at which the identical residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window and multiplying the result by 100 to yield the percentage of sequence identity. Total identity is then determined as the average identity over all of the windows that cover the complete query sequence. Although not wanting to be bound by theory, computer software packages such as GAP, BESTFIT, BLASTA, FASTA and TFASTA can also be utilized to determine sequence identity.

This definition could be used by one of skill in the art to determine which sequences are included in the "95% identical to SEQ ID NO:1" genus.

Referring to Lilly, it is stated that a generic statement which does not distinguish the genus from others, except by function, is not adequate. In the language of Claim 15, as amended, the genus is distinguished by structure, not function. Lilly goes on to state that a genus described only by function does not allow one of ordinary skill in the art to visualize or recognize the identity of the members of the genus. In contrast, the genus recited in Claim 15 ***can be visualized*** by one skilled in the art. From the term "nucleotide sequence", it is clear that the structure is a polymer made up of a ribose and phosphate backbone with variable side groups of adenine(A), cytosine(C), guanine(G), and thymine(T). Any given base pair in the sequence could be one of these nucleotides, but no other structure. An additional limitation is that the sequence must be 95% identical to SEQ ID#1 or SEQ ID#2, and 95% identity is expressly defined in paragraph [0051] of the specification.

With regard to the Enzo standard, Applicants submit that Claim 15 does, in fact, describe relevant identifying characteristics including structure, physical properties, and functional characteristics. The claim defines the structure as "comprising a nucleotide sequence 95% identical to SeqID#1 or a sequence at least 95% identical to SeqID#2." The claim, as amended, defines the physical properties in that the sequence is stated to be a nucleotide sequence. Nucleotide sequences have well-known and well characterized physical properties. Finally, the claim describes the function of SEQ ID#1 and SEQ ID#2, because the sequences are identified in the specification as sequences which would be found in two Ad5 viruses. One of skill in the art would have known, or could have learned from reading the specification, that these viruses selectively replicate in cancer cells with p53 gene mutation, and thus lyse cancer cells with high specificity (please see [0063]).

Applicants submit that Claim 15, as amended, adequately describes the claimed subject matter and that this claim is therefore in condition for allowance.

III. CLAIM REJECTIONS UNDER 35 USC §102

A. The Examiner has rejected Claims 1 and 12-14 on the grounds that they are anticipated by Ries et al. 2002, January 7, Br. J. Cancer 86(1):5-11 ("the Ries Reference"). The Examiner states that the term "stimulus" can be interpreted to encompass a chemotherapeutic agent, and that in this sense the Ries Reference discloses the claimed material of the current application.

In response, Applicants have amended Claim 1 to further emphasize the distinguishing properties of the invention. This amendment finds support throughout the specification, and in paragraphs [0020], [0025], [0027], [0042], and [0067].

Claim 1, as amended, clearly defines the stimulus which is applied to the tumor cells described in the method. The stimuli recited in the claim are distinct from the chemotherapeutic agents which are disclosed in the cited reference. Therefore, the Ries Reference cannot anticipate the current claim.

Applicants respectfully submit that Claim 1, and dependent Claims 12 and 14, are in condition for allowance.

B. The Examiner has rejected Claims 1, 10, 12-14, and 19, on the grounds that they are anticipated by U.S. Patent No. 6,080,578 ("the '578 Reference"). The Examiner states that the '578 Reference discloses identical subject matter to the claimed material in that it describes a mutant virus which is capable of replicating to a much greater degree in cells lacking p53 function and that the adenoviral therapy of the invention may be combined with other protocols such as chemotherapy.

As described above, Claim 1 has been amended to describe species of stimuli. The stimuli recited in this claim do not include the administration of a chemotherapeutic agent, as is taught in the '578 Reference. Therefore, the '578 Reference cannot anticipate the current claims.

Applicants submit that Claim 1, and dependent Claims 10, 12-14, and 19, are, therefore, in condition for allowance.

C. The Examiner has rejected Claim 1 on the grounds that it is anticipated by U.S. Patent Publication No. 2002/0006914, published January 17, 2002 ("the '914 Reference"). The

Examiner states that the '914 Reference anticipates the current claims in that it discloses the introduction of a gene into tumor cells which causes increased sensitivity to cancer therapy in the cells.

As described above, Claim 1 has been amended to recite specific stimuli which may be applied to tumor cells in the disclosed method. These stimuli do not include the techniques taught in the '914 Reference.

Moreover, the '914 Reference discloses introduction of a gene which is non-therapeutic and subsequent treatment with a therapeutic agent, the effect of which is strengthened by the prior therapy-sensitizing gene. The current claims recite contacting the tumor with a lytic agent, which ***is*** therapeutic for treatment of the cancer. Cells in the current claims are also subjected to an in vivo stimulus, which may be non-therapeutic. Therefore, the purpose of the introduction of a gene or lytic agent in the current claims is actually therapeutic, which is not the case in the '914 Reference, wherein the gene is supplied only for the purposes of strengthening the effect of a therapeutic agent.

Applicants respectfully submit that the '914 Reference does not anticipate Claim 1, as amended. Therefore, Claim 1 is in condition for allowance.

IV. CLAIM REJECTIONS UNDER 35 U.S.C. §103

A. The Examiner has rejected Claims 27-28 under 35 U.S.C. §103, as being unpatentable over the Ries Reference in view of Yosef et al. (2001, Cancer Research 61:8361-8365, "the Yosef Reference"). The Examiner states that the Ries Reference discloses the limitation of Claim 27, describing an elevated level of a chaperone protein in the stimulated tumor. The Examiner further states that the Yosef Reference teaches that heat shock proteins enhance the oncolytic effect of a replicative adenovirus, and the use of an adenoviral vector that has been modified to express an hsp70 protein.

As described above, the Ries Reference teaches an adenovirus capable of being expressed preferentially in tumors. However, the current invention comprises a more complex method of treating tumor cells, which involves the addition of a specific stimulus in order to achieve a desired therapy. Although the Ries Reference refers to increased anti-tumor efficacy of ONYX-

015 when combined with the specific chemotherapeutic agent 5-FU, it does not describe the method of the current application, which provokes a response by using any of a number of stimuli. In fact, synergy between ONYX-015 and 5-FU would not be expected to predict synergy between ONYX-015 and any other agent.

Claim 1, from which Claims 27 and 28 depend, has been amended to recite specific stimuli which may be used in the method. These specific stimuli do not include the use of chemotherapeutic agents, further differentiating the claim from the Reis Reference.

Moreover, the Ries Reference discloses a method for increasing the lytic effect of an oncolytic virus by promoting adenovirus replication using HSPs. The current claims describe a method of using HSPs to form HSP-cancer antigen complexes, not increasing adenovirus replication. Applicants have amended Claim 27 to emphasize the formation of HSP-cancer antigen complexes.

The Yosef Reference teaches that heat shock protein and heat shock protein (inducible) enhance the oncolytic effect of replicative adenovirus. However, the Yosef Reference does not teach the method of current claims, which involves applying one or more specific stimuli after the delivery of a lytic agent. The Yosef Reference discloses only the treatment of cells by placing them in a 42.5°C incubator, rather than a local increase in temperature in a subject or a whole-body temperature increase as described in the current claims. All of the experiments carried out in this reference were conducted in cell lines, rather than in a subject as in the currently claimed methods.

Therefore, the neither the Reis Reference nor the Yosef Reference, alone or in combination, would have rendered the currently claimed material obvious to one of skill in the art.

Applicants therefore respectfully submit that Claims 27 and 28 are in condition for allowance.

B. The Examiner has rejected Claims 4-8 under 35 U.S.C. §103 as being unpatentable over the Reis Reference. The Examiner states that the Reis Reference discloses a method for

ablating tumor cells, which also comprises applying conventional dosing regimens for administration of an adenovirus.

As described above, Claim 1, from which Claims 4-8 depend, has been amended, and no longer recites a chemotherapeutic agent among the claimed stimuli. In light of this amendment, Claims 4-8 would not have been obvious in view of the Ries Reference.

Applicants therefore respectfully submit that Claims 4-8 are in condition for allowance.

C. The Examiner has rejected Claims 27-28 under 35 U.S.C. §103 as being unpatentable over the '578 Reference in view of the Yosef Reference.

Claims 27-28, in light of the amendment to Claim 1, do not recite a chemotherapeutic agent among the possible stimuli. These claims are therefore not obvious in view of the '578 Reference alone or in combination with the Yosef Reference.

Applicants therefore respectfully submit that Claims 27-28 are in condition for allowance.

D. The Examiner has rejected Claims 4-8 under 35 U.S.C. §103 as being unpatentable over the '578 Reference.

As discussed above, the '578 Reference describes a method which comprises the use of a chemotherapeutic agent, which in not included in the method described here. Nor would it have been obvious to use any of the named stimuli in the current claims in place of a chemotherapeutic agent, since their methods of action are known to be distinct. Therefore, the Claims 4-8 would not have been obvious in view of the '578 Reference.

Applicants therefore respectfully submit that Claims 4-8 are in condition for allowance.

E. Claims 2-3, 9, 10 and 20 have been rejected under 35 U.S.C. §103 as being unpatentable over the '914 Reference in view of Qi et al. (2001, Int. J. Hyperthermia 17(1):38-47; "the Qi Reference"). The Examiner states that the '914 Reference discloses a method for

ablating tumor cells, and that the Qi Reference teaches the use of a similar method for the treatment of nasopharyngeal carcinoma.

Applicants respectfully traverse this argument. As described above, Claim 1, from which Claims 2-3, 9, 10 and 20 depend, has been amended, and does not recite the techniques for stimulating a cell which are taught in the '914 Reference.

The Qi Reference teaches the treatment of a cell line, not a subject as described in the current claims. In addition, this reference discloses treatment of cells by placing them in a 43°C incubator, rather than a local increase in temperature in a subject or a whole-body temperature increase as described in the current claims.

Therefore, neither the '914 Reference nor the Qi Reference, alone or in combination, could have rendered the currently-claimed material obvious to one of skill in the art.

Applicants submit that Claims 2-3, 9, 10 and 20 are therefore in condition for allowance.

V. CONCLUSIONS

Applicants respectfully submit that, in light of the foregoing amendment and comments, Claims 1-10, 12-15, 19, 20, 27 and 28, and newly added Claims 62-65 are all in condition for allowance. A Notice of Allowance is therefore requested. If the Examiner has any other matters which pertain to this Application, the Examiner is encouraged to contact the undersigned to resolve these matters by Examiner's Amendment where possible.

Respectfully submitted,

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